REMARKS

Following entry of the foregoing amendments, claims 120, 121, 124, 127, and 136 to 138 will be pending in this patent application. Claim 120 has been amended herein, without prejudice. No claims have been canceled, and no new claims have been added. Support for the amendments is found throughout the specification as originally filed, including, for example, paragraphs 118, 120, 104, 105, and 122, and the amendments therefore do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 120, 121, 124, 127, and 136 to 138 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Wyatt, *et al.*, *Nucleic Acids Res.*, 1989, 17, 7833-7842 ("the Wyatt article"), Manche, et al., *Mol. Cell Biol.*, 1992, 12, 5238-5248 ("the Manche article"), Monia, *et al.*, *J. Biol. Chem.*, 1993, 268, 14514-14522 ("the Monia article"), and European patent application publication number EP 0339842 ("the Shibahara application"). Applicants respectfully request reconsideration and withdrawal of this rejection because, as discussed repeatedly during prosecution of this application, those of ordinary skill in the art would have had no reason to design and produce the claimed oligomeric compounds at the time of the invention.

This application has been pending since November, 2003. In the ensuing seven years, claims in this and related applications have been serially rejected under 35 U.S.C. §§ 112, 101, 102, and most recently, 103. Applicants have repeatedly replied at great expense to office action after office action, overcoming one set of rejections, only to be confronted with a new set. In response to the previous rejections under 35 U.S.C. § 103, applicants provided a Declaration from Dr. David Corey, a noted scientist who has been active in the field since the time of the original filing. Dr. Corey's declaration sets forth in detail the factual basis for why one of skill in the art would not have found the claimed oligonucleotides obvious. The Office dismissed this declaration, however, simply labeling it non-persuasive. Hoping at long last to resolve this application, applicants then appealed to the Board of Patent Appeals

and Interferences and submitted a request for a pre-appeal brief conference that also sets forth in detail why the claimed oligonucleotides would not have been obvious at the time of the invention. After the notice of appeal and request for a pre-appeal brief conference were filed, rather than allowing the claims, or even allowing the application to proceed to appeal to finally resolve the outstanding issues, the Office instead re-opened prosecution, with allegedly "new" grounds for once again rejecting the claims as obvious. The present rejections rely on several references already addressed by the applicants and discussed by Dr. Corey in his declaration. Those previously discussed references are now combined with new, largely duplicative references, not previously cited throughout the long prosecution history of this application. As explained below, these "new" rejections fail for the same fundamental reason as the appealed rejections: the Office has still not provided a reason why one of skill in the art would have made the claimed oligonucleotides prior to invention by the applicants.

Because obviousness must be analyzed as of the time that an invention was made, it is imperative that the Patent Office avoid resorting to hindsight when assessing obviousness.[1] To avoid relying on hindsight, the Office must therefore demonstrate that the cited prior art reference or combination of references teaches or suggests all the limitations of the claims.[2] And rejections under § 103 must also be supported by "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does*."[3]

Those of ordinary skill in the art would not have had any reason to design and produce the claimed oligonucleotides before applicants' invention in view of the description provided in the cited references and the state of the art at that time. Specifically, those of ordinary skill in the art would not have had a reason at the time of the invention to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second

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[1] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, 1742 (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").
[2] *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).
[3] *Id.* (emphasis added).

oligonucleotide comprises at least one 2'-sugar modification, in view of the description provided in the cited references.

In this regard, the Wyatt article does not describe or suggest fully complementary oligonculeotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification, and nothing in the Wyatt article would have prompted those of ordinary skill in the art to produce such duplexes. Rather, the Wyatt article describes duplexes of complementary 14-mer oligoribonucleotides, and also describes 14-mer oligoribonucleotide duplexes in which one or two 2'-deoxyribonucleotides were substituted for the ribonucleotides in one or both of the strands. The duplexes were used in *in vitro* experiments aimed towards determining the structural requirements of RNase V_1. In these experiments, the oligoribonucleotide duplexes and deoxy-substituted duplexes were incubated *in vitro* with the RNase V_1 and buffer, and the article reports that the deoxy substitutions reduced cleavage by RNase V_1. Significantly, no other ribonucleases were present during the RNase V_1 reactions.

The Wyatt article also describes experiments designed to determine the structural requirements for *E. coli* RNase H that utilized 14-mer oligoribonucleotides with or without one or two 2'-deoxyribonucleotide substitutions hybridized to complementary 17-mer deoxyoligoribonucleotides or hybridized to complementary 17-mer oligoribonucleotides having one or two 2'-deoxyribonucleotide substitutions. In the RNase H reactions, the substrates were incubated *in vitro* with RNase H and buffer, and the reactions did not contain any other ribonucleases. The article indicates that deoxy substitutions in the RNA strand of the RNA:DNA hybrids inhibited cleavage by RNase H. Significantly, the Wyatt article provides no teaching or suggestion that would have prompted those skilled in the art to produce oligonucleotide duplexes in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification. Nothing about the design or nature of the experiments described in the Wyatt article would have provided a reason to introduce sugar-modified nucleosides into *both* strands of an oligonucleotide duplex.

The remaining references fail to supply this missing teaching or suggestion, and thus fail to compensate for the deficiencies of the Wyatt article. In this regard, as discussed at

length previously during prosecution of this application, and as explained by Dr. Corey in his declaration,[4] the description provided in the Manche article would not have prompted one of ordinary skill in the art to introduce 2'-sugar modifications into *both* strands of an oligonucleotide duplex. Instead, the Manche article describes short RNA duplexes that were used as substrates in experiments designed to elucidate the mechanism of activation of interferon-induced protein kinase DAI. Specifically, the experiments involved binding DAI to RNA duplexes of 15, 23, 34, 40, 55, 67, 85, or 104 nucleotides *in vitro*.[5] The RNA duplexes were not chemically modified, and as pointed out by Dr. Corey in his declaration,[6] nothing about the nature or aim of the experiments described in the Manche article provides any reason that would have prompted those of ordinary skill in the art to produce chemically modified RNA duplexes, much less duplexes having at least one sugar-modified nucleoside in both strands, as presently claimed.

The Monia article also fails to provide this missing teaching or suggestion. Instead, the Monia article describes 17-mer oligonucleotides having a central gap region of 2'-deoxynucleotides and having 5' and 3' wing regions of 2'-OMe substituted nucleotides.[7] These gapmers were hybridized to the following complementary RNAs:

1. A synthetic, end-labeled 25-mer RNA corresponding to Ha-*ras* RNA. The resulting duplex was used in *in vitro* melting experiments;

2. A 47-mer Ha-*ras* RNA hairpin. The resulting duplex was used in *in vitro* RNase activation experiments; and

3. Full-length Ha-*ras* mRNA, after introduction of the gapmer into HeLa cells that had been transfected with an Ha-*ras* expression plasmid, to determine the antisense activity of the gapmer.

The Monia article also describes hybridization of 11-mer, 13-mer, or 15-mer 2'-OMe gapmers to end-labeled 25-mer RNAs corresponding to Ha-*ras* RNA. The resulting duplexes was used in *in vitro* melting experiments.[8]

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[4] Declaration of Dr. David Corey filed August 18, 2009, paragraphs 16 to 19.
[5] Figure 1A.
[6] *Id.*
[7] Figure 1
[8] Figure 8A.

Finally, the Monia article describes melting experiments that utilized 17-mer gapmers having a central, 2'-deoxy region and 5' and 3' wing regions of either 2'-deoxy, 2'-O-pentyl, 2'-O-propyl, 2'-O-methyl, or 2'-fluoro groups hybridized to 25-mer RNAs corresponding to Ha-*ras* RNA.[9] These gapmers were also introduced into HeLa cells that had been transfected with an Ha-*ras* expression plasmid to determine their antisense activity against full-length Ha-*ras* mRNA.

Significantly, the Monia article contains no teaching or description that would have prompted those of ordinary skill in the art to incorporate at least one modified sugar into *both* strands of an oligomeric compound duplex. The *in vitro* melting and RNase activation experiments described in the Monia article utilized duplexes in which only one strand contained chemical modifications, and there would have been no reason to utilize substrates having chemical modifications in both strands in such experiments. Furthermore, in the experiments in which the antisense activity of the single-stranded gapmers was analyzed, *duplexes* were not introduced into HeLa cells, but, rather, single-stranded gapmers were introduced, and their activity against unmodified, full-length mRNA target was determined. Accordingly, nothing about the design or objective of the experiments described in the Monia article would have prompted those of ordinary skill in the art to incorporate chemical modifications into both strands of an oligonucleotide duplex, much less incorporate 2'-modified wings into the first oligonucleotide and at least one 2'-sugar modification into the second oligonucleotide, as presently claimed.

Finally, the Shibahara application also fails to provide such a reason, but instead describes *single-stranded* antisense ribooligonucleotides targeted against HIV genomic RNA or against HIV DNA integrated into a chromosome.[10] The Shibahara application describes experiments in which such single-stranded antisense ribooligonucleotides were introduced into cells that had been infected with HIV, and the cytopathic inhibitory effect of the ribooligonucleotides was determined.[11] Although the Shibahara application describes chemical modification of the antisense ribooligonucleotides, including 2'-OMe

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[9] Table II.
[10] Page 3, lines 36 to 46 and page 14, lines 44 to 46.
[11] Page 18, lines 11 to 36 and experimental example 7, page 27, line 26 to page 30, line 33.

modifications,[12] the Shibahara application does not describe or suggest any reason to introduce chemical modifications into oligonucleotide *duplexes*.

Those of ordinary skill in the art would therefore have had no reason to produce duplexes of fully complementary oligonucleotides consisting of 17 to 25 linked nucleosides in which the first oligonucleotide is a gapmer having 2'-modified wings and the second oligonucleotide comprises at least one 2'-sugar modification before applicants' invention in view of the description provided in the cited references, when considered in combination in view of the state of the art at that time. The claimed oligonucleotides therefore would not have been obvious before applicants' invention.

The Office asserts, however, that those skilled in the art would have introduced 2'-OMe modifications into both strands of oligonucleotide duplexes used for testing "as substrates for various dsRNases" to protect the oligonucleotide duplexes from "unintended nuclease degradation."[13] Contrary to the Office's assertion, those of ordinary skill would *not* have had a reason to incorporate chemical modifications, such as 2'-sugar modifications, into *both* strands of oligonucleotide duplexs used as dsRNAse substrates at the time of the invention because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred. In the *in vitro* experiments described in the references, such as the RNase H and RNase V_1 digestion experiments, in accordance with the experimental designs used, undesired nucleases were not present during the reactions that could have potentially degraded the substrates. As discussed above, only the RNase H and RNase V_1 endonucleases were present in the reaction mixtures, and no other enzymes were present. Furthermore, in the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts, *single-stranded* oligonucleotides targeted against full-length mRNAs or genomic RNAs were used in such experiments, and double-stranded duplexes were not utilized. None of the references therefore describes experiments in which double-stranded nucleic acids were introduced into an environment in which undesired nucleolytic degradation of the duplexes could have occurred. Accordingly, contrary to the Office' assertion, the cited references fail to provide any reason that would have prompted those of ordinary skill in the art to protect both strands

[12] Page 4, lines 1 to 53.
[13] Office action dated July 14, 2010, page 7.

of an oligonucleotide duplex of the length claimed against nucleolytic degradation by introducing chemical modifications into both strands of such duplexes. Dr. Corey explained that such compounds would not have been particularly suitable for the research described in the previously cited references, including the Manche article. Likewise, there would have been no reason why one skilled in the art would have used such compounds for the research described in the additional, newly-cited references. Because none of the cited reference, nor all of them combined, describe research for which one skilled in the art would have had a reason to make the claimed oligonucleotides, such compounds would not have been obvious at the time of the invention.

By submitting this reply, applicants are yet again responding to the assertions made in the official action in effort to resolve all of the outstanding issues for this application so as to advance it to allowance. Applicants again, accordingly, respectfully request withdrawal of the rejection for alleged obviousness.

Alleged Double Patenting

Claims 120, 121, 124, 127, and 136 to 138 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, and 130 to 156 of copending U.S. patent application number 10/859,825 in view of the Wyatt, Manche, and Monia articles and the Shibahara application. Claims 120, 121, 124, 127, and 136 to 138 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 86 to 123 of copending U.S. patent application number 10/701,264 in view of the Wyatt, Manche, and Monia articles and the Shibahara application. Without conceding the correctness of these rejections, applicants request that they be deferred pending the identification of allowable subject matter in the present application, as the rejections can likely be readily resolved, depending upon the subject matter ultimately allowed, through the filing of suitable terminal disclaimers.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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